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NUTRITION REVIEWS

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November 1944

The Future of Nutritional Research..... 321
Amino Acids and Plasma Protein Production..... 322
Prescribed Diets for Normal Children..... 323
Serum Tocopherol in Muscular Dystrophy..... 324
Nutritional Role of Cholesterol in Coronary Arteriosclerosis..... 325
Nutrition and Rheumatic Fever..... 327
Dietary Thiamin Levels and Deficiency Symptoms..... 328
Histidine Deficiency in Man..... 330
Serum Phosphatase Activity and Rickets..... 331
Protein Requirement in Hot Environments..... 332
Deficiency Anemia in Infants..... 333

(Continued on Back Cover)

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NUTRITION REVIEWS

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THE FUTURE OF NUTRITIONAL RESEARCH

On undertaking to write this editorial it occurred to me to read the dictionary definition of nutrition. Funk and Wagnalls New Standard Dictionary, 1928, defines the word nutrition as "the process by which growth is promoted and waste repaired in living organisms." It would appear that space might have been saved by omitting the word "living." A helpful explanatory note reads: "This process is preceded by chemical changes involved in digestion, absorption, and assimilation of food through the mucous membrane of the alimentary canal, and the transference of the nutriment to the required place by the blood and lymph." Considering the state of our knowledge in 1928, this definition and note do not now sound appropriate, but it does make clear the progress which we have made since about 1900 in the study of nutrition. We have achieved considerable success in discovering the number and natures of the simple chemical substances which, when ingested in appropriate amounts at proper intervals, constitute an adequate diet. We have learned a great deal about what nutriment consists of.

We are still as much interested as was the lexicographer in digestion, absorption, and the transference of the nutriment to the required place by the blood and lymph. We would extend the sites of assimilation from the mucous membrane of the alimentary tract to every tissue which is nourished by the absorbed nutrients. The nutrition investigator now has interest in more details than anyone of three decades ago ever dreamed. We can enumerate fairly accurately the kinds of investigations which must be completed in order to provide a comprehensive knowledge of nutrition, a branch of learning which forms a part of the science of biochemistry. If we were to try to segregate those items which are indispensable to a complete understanding of the attainment of the objective of securing the optimum state, or the highest perfection of nutrition in any species, we should arbitrarily have to restrict our definition of nutritional research to inquiry concerning:

(1) The number and natures of the amino acids, fatty acids, carbohydrates, inorganic substances, and all other chemical substances now loosely grouped together for convenience under the term vitamins.

(2) The occurrence of these nutrients in plant and animal products. This is necessary to an understanding of the nature and extent of our food resources, the planning of diets, and the study of the economics of food production.

(3) The stability of each of the essential nutrients under such conditions as are necessary in the harvesting, storage, and handling of foods and their preparation for serving. Such studies are fundamental to safeguarding the quality of diets for man or feeds for animals.

(4) The influence of the diet, whether of constant character or changed at successive intervals, on the character and abundance of the microscopic flora and fauna of the alimentary tract, and its relation to the health of the host.

(5) The relation of stage of maturity in plants to their nutritive value.

(6) The interrelations between the various nutrients by which they exert a synergistic action or otherwise affect the biochemical behavior of each other.

(7) The nature and extent to which any essential nutrient may arise through the synthetic powers of the body provided the necessary precursor is provided.

(8) The effect of the several indispensable inorganic elements and the forms in which they are ingested on the absorbability of each of them from the alimentary tract.

(9) The symptoms which make manifest

to the eyes of the trained observer the existence of deficiency of an essential nutrient in the diet of man or animal. These include physical, anatomical, and physiologic responses to any type of nutritional aberration.

(10) The further development of laboratory technics by means of which foods may be analyzed for their contents of essential nutrients; also the development of laboratory methods for determining the content of essential nutrients in tissues and excreta.

(11) The influence of light, temperature, humidity, and atmospheric pressure on the body's need for nutriments, and the optimum composition of the diet under special environmental conditions.

(12) The relation of the diet to the development of immunity to disease.

(13) The minimal needs of the body under specified conditions for each of the essential nutrients and the determination of whether an excess of any nutrient over the minimum physiologic needs affords a factor of safety. If so, what is the minimal margin of safety which should be provided under specified conditions of work, physical environment, etc.

Additions could be made to this list of fields for study which would contribute to knowledge of nutrition, but these will suffice to describe the general vista which lies ahead. Each of these fields of study has a practical aspect. Every item of knowledge of nutrition has a bearing on practical application of other facts to human and animal nutrition.

The conscientious and sensitive biochemist with interest and enthusiasm for nutrition studies will not be satisfied with the dictionary's declaration that the process of nutrition ends with "the transference of the nutriment to the required place by the blood and lymph." He will not be willing to rest contented after the nutriment is dumped at the terminals reached by these fluids. In fact he is now convinced that it is at this boundary that the most interesting chemical processes begin. He will not rest until he has explored, by every device of which he can think, the processes of nutrition during the phases of assimilation of absorbed nutrients into functioning tissues, the chemistry of intermediary metabolism, and the disposal of the end products of metabolic activity.

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AMINO ACIDS AND PLASMA PROTEIN PRODUCTION

Stimulated by the problems arising through warfare and pointed up by the striking benefit in the treatment of infections resulting from the use of sulfonamides and penicillin, problems of tissue repair are coming to the fore. Tissue injury whether by physical trauma, burns, infection, or major surgical procedures is associated with nitrogen losses which may be large. The repair of the tissue damage, furthermore, necessitates drawing upon preexisting reserves of body protein unless the oral intake of protein is very good. Patients with low reserves have less to draw upon and consequently healing is poor. Therefore, it is important to know in detail what factors are concerned in the building up of body proteins and to discover means of administering them efficiently and in large quantities.

Madden and Whipple (*Physiol. Rev.* **20,** *194 (1940)*) have given reasons indicating that plasma protein is not static but reflects tissue stores. The factors concerned with the formation of plasma protein are, therefore, pertinent to the problem of tissue repair. As discussed in a previous review (*Nutrition Reviews* **1,** *200 (1943)*) dietary factors are important for the formation of plasma proteins. Madden, Woods, Shull, and Whipple (*J. Exp. Med.* **79,** *607 (1944)*)

offer data indicating the role of amino acid mixtures in the production of plasma protein.

Their method of study corresponds to the method whereby Whipple and co-workers studied the value of various dietary factors in hemoglobin production. Dogs were first standardized by body protein and plasma protein depletion through diet restriction and plasmapheresis. A depleted state was reached in which the kind or the quantity of the diet intake was fairly directly responsible for the size of the plasma protein removal (by plasmapheresis) necessary to maintain the depleted level. To such dogs various mixtures of crystalline amino acids were fed or were given parenterally in fresh solution after dissolving in boiled hot distilled water.

The value of various mixtures was determined by comparing the plasma protein nitrogen removed by plasmapheresis with the amino acid nitrogen fed or injected. The latter represented more than 20 per cent of the former when the better amino acid mixtures were used.

These studies showed that the ten growth essential amino acids of Rose plus glycine will maintain nitrogen balance and produce as much new plasma protein as will good diet proteins. This good utilization was demonstrated over periods of several months and occurred whether the amino acids were given orally or parenterally. The mixture which was most efficient and the amounts which were regarded as a minimum for a dog weighing 10 kg. consisted, in grams, of dl-threonine 0.7, dl-valine 1.5, l-(−) leucine 1.5, dl-isoleucine 1.4, dl-lysine hydrochloride 1.5, l (−) tryptophane 0.4, dl-phenylalanine 1.0, dl-methionine 0.6, l (+)-histidine hydrochloride 0.5, l (+)-arginine hydrochloride 0.5, and glycine 1.0. The presence of glycine improved tolerance to rapid intravenous injection, but excess glycine did not improve utilization of the mixture. Over a long period this mixture appeared to be suboptimal in quantity but double this amount was more than ample.

It is noteworthy that mixtures of these amino acids were well tolerated even upon rapid injection. The mixture here listed could be given intravenously in ten minutes without reaction. Subcutaneously a 10 per cent solution could be given rapidly without reaction. There was no evidence of toxicity in general nor to unnatural forms of synthetic amino acids in particular. Bassett, Woods, Shull, and Madden (*New Engl. J. Med.* **230,** *106 (1944)*) have found this to be true also in a human subject, and the vomiting and pyrogenic effects noted previously when an amino acid mixture was used which contained more of the nonessential amino acids, were not encountered.

A casein digest prepared by enzymatic hydrolysis provided good nitrogen retention and fairly good plasma protein production, but was much less tolerable upon intravenous injection than certain mixtures of pure amino acids. Another casein digest prepared by acid hydrolysis to which tryptophane was added, afforded bare nitrogen equilibrium but produced virtually no plasma protein.

PRESCRIBED DIETS FOR NORMAL CHILDREN

By overemphasis of the details of man's food requirements, enthusiastic students of nutritional science sometimes confuse rather than clarify the practical application of lessons learned, creating a situation in which it is often difficult to see the forest for the trees. For the average parent, dietary advice in terms of vitamins and mineral requirements is confusing; and overemphasis on separate nutrient factors, to physicians as well as to parents, may lead to needless or unsound bolstering of a dietary regimen with pharmaceutical preparations. On the other hand, it is not enough merely to tell parents that a

child should have "lots of milk, meat, eggs, vegetables, and fruits."

Following a middle ground between such alternatives, but with full attention to both quantitative and qualitative aspects of dietary intakes, Boyd (*J. Pediatrics* **24,** *616 (1944)*) cites the recommendations of the Food and Nutrition Board of the National Research Council in formulating a few principles for advice on the diets of normal children. These recommendations, designed with optimal nutrition as a goal, of course take into consideration the progressive alteration of need with advancing maturation. "It is refreshing to discover that all the elements of a complete diet can be provided in adequate amounts solely through the use of simple foodstuffs if one properly includes fish liver oil among the foods."

In two well designed diagrams, Boyd illustrates how quotas of nutritional essentials specified in the National Research Council recommendations for a child 10 to 12 years of age are met by a proposed daily diet that includes only foods generally available throughout all seasons of the year. Also, he compares the ingredients of a sample "prevalent" diet of a 10 year old child with the ingredients of a prescribed optimal diet. Although superficially not very different from the optimal diet, the "prevalent" sample diet fails to meet the National Research Council recommendations in respect to calories, protein, vitamin A, ascorbic acid, and vitamin D. By only slight increases, especially in the intake of milk, eggs, and meat, and the inclusion of 1 teaspoonful of cod liver oil, all essential nutrient factors in the sample diet could be raised to above the standard requirements. An essential in any plan of this sort for prescribing of diets is advice on the proper preparation of foods to conserve their vitamin content; e.g., cooking of potatoes in their skins and peeling them just before serving. Commenting on the inclusion of 75 g. of sugar in the prescribed diet (not holding with those who believe that sugar need be restricted to avoid tooth decay), Boyd points out that the child who receives a diet which qualitatively and quantitatively is complete has much less desire for sweets than the child whose nutritional pattern is deficient.

If there is rebellion against overemphasis on the minutiae of nutritional requirements, and against too rigid dietary prescription, it may be well to remember the experiments of Davis (*Am. J. Dis. Child.* **36,** *651 (1928)*) with self-selection of diets by children. Her results, showing that children would voluntarily select a well balanced diet from a large variety of foods offered at each meal, might encourage laxity in the prescribing of diets; but emphasis now is placed on the fact that foods must be made available if they are to be eaten. Loosely phrased recommendations are apt to provide less economical diets than specific prescription of minimal amounts of the important items of a proposed dietary.

SERUM TOCOPHEROL IN MUSCULAR DYSTROPHY

The discovery that vitamin E is involved in the normal development and metabolism of skeletal muscles (Pappenheimer, *Physiol. Rev.* **23,** *37 (1943)*) led to the hope that some of the muscle disorders occurring in man might be relieved by the administration of this vitamin. This hope was fortified by the observation that creatinuria occurs in association with vitamin E deficiency in animals as well as in certain muscle disorders in man. The creatinuria in deficient animals ceases when vitamin E is administered.

Clinical trials, however, have been disappointing and have not confirmed the early hopeful observations of Bicknell (*Lancet* **I,** *10 (1940)*). Nevertheless, to Minot and Frank (*Am. J. Dis. Child.* **67,** *371 (1944)*) it seemed possible that lack

of therapeutic effect did not rule out the possibility of a deficiency secondary to some anomaly of absorption or excretion of the vitamin or to chemical destruction of biologically active tocopherol. They consequently undertook to supplement their therapeutic trials with comparative quantitative determinations of the concentrations of tocopherol in the blood sera of boys with pseudohypertrophic muscular dystrophy and of normal children of similar age.

The colorimetric method described by Emmerie and Engel (*Rec. d. trav. chim. d. Pays-Bas* **58,** *895* (*1939*)) as modified by Mayer and Sobotka (*J. Biol. Chem.* **143,** *695* (*1942*)) and by Devlin and Mattill (*Ibid.* **146,** *123* (*1942*)); and Hines and Mattill (*Ibid.* **149,** *549* (*1943*)) was used. This depends on photoelectric measurement of the color produced when ferric iron is reduced by tocopherol in the presence of α-α-dipyridyl. The reaction is not specific, but seemed worth using since the color produced by extracts of serum from animals with vitamin E deficiency was slight and increased promptly with the administration of tocopherol.

As subjects for the study, 8 boys with typical pseudohypertrophic muscular dystrophy ranging in age from 5 to 19 years were used. The degrees of disability varied through the ranges observed in this disorder. These patients were treated with a considerable variety of preparations containing vitamin E, crude forms as well as alpha-tocopherol. Oral and parenteral therapy were employed. Although little is known in regard to the dietary requirements for vitamin E, one would think that the doses given were sufficiently large to correct a deficiency if such existed.

The "tocopherol" content of the blood serum of untreated patients with muscular dystrophy ranged from 0.73 to 1.28 mg. per 100 ml. while that of children of similar age without muscular disease was 0.64 to 1.12 mg. per 100 ml. Following the administration of vitamin E to the patients there was a prompt and significant rise in the level of tocopherol, amounting to an increase of 20 to 50 per cent. Nevertheless, no significant clinical improvement occurred and no change in the degree of creatinuria took place.

These results are disappointing to those who are seeking some clue in attacking this strange condition. It seems that patients with muscular dystrophy have neither a primary lack of vitamin E nor a deficiency secondary to poor absorption or chemical destruction of tocopherol. As Minot and Frank point out, however, it is still conceivable that there exists in this disorder some interference with intermediate steps in the utilization of alpha-tocopherol which might block the postulated effectiveness of this vitamin in relieving the muscular dystrophy.

NUTRITIONAL ROLE OF CHOLESTEROL IN CORONARY ARTERIOSCLEROSIS

There have been repeated suggestions that hypercholesteremia plays an etiologic role in the production of atherosclerosis and, therefore, in the pathogenesis of arteriosclerosis of the coronary arteries. This relationship is particularly clear in xanthomatosis. It is conceivable that hypercholesteremia may also explain in part the increased incidence of arteriosclerotic changes in hypothyroidism (Bruger and Rosenkrantz, *J. Clin. Endocrinology* **2,** *176* (*1942*)) and in diabetes mellitus (Root, Bland, Gordon, and White, *J. Am. Med. Assn.* **113,** *27* (*1939*)). A number of investigators, however, have denied that the degree of atherosclerosis is related to hyperlipemia or to the level of serum cholesterol (Landé and Sperry, *Arch. Path.* **22,** *301* (*1936*)); Page, *Ann. Int. Med.* **14,** *1741* (*1941*)). The effect of dietary cholesterol,

in the absence of any endocrine dysfunction, has been even more difficult to evaluate. Herbivorous animals (rabbits), when fed an excess of cholesterol, do apparently develop hypercholesteremia and atheromatous changes in their vessels (Leary, *Arch. Path.* **32,** *507 (1941)*). After esterification of cholesterol in the liver, the excess esters are phagocytized by reticulo-endothelial cells which escape into the circulation and invade the arterial intima. These changes do not develop under similar circumstances in carnivorous animals, presumably because cholesterol is metabolized more efficiently. Interpretation is further complicated by the claim that the atherosclerotic lesion produced in rabbits by the feeding of cholesterol is not identical with that of human arteriosclerosis (Duff, *Arch. Path.* **20,** *81, 259 (1935)*).

The opportunities for observing the effect of increased ingestion of cholesterol in human subjects over a long period of time are obviously limited. While many patients with arteriosclerotic heart disease do have elevated blood cholesterol levels, this is apparently not always the case. Grotel and co-workers (*J. Am. Med. Assn.* **114,** *2345 (Abst.) (1940)*), however, concluded from a study of human pathologic material that there was a definite correlation between the development of arteriosclerosis and excessive intake of cholesterol. Exactly the opposite conclusion has been reached by Shaffer at the Henry Ford Hospital (*Ann. Int. Med.* **20,** *948 (1944)*).

Shaffer selected 100 patients who had been under treatment for duodenal ulcer for from five to thirty-five years (average twelve and a half years). Ninety-five per cent were males. Since these patients had all been given milk and cream in large amounts they had all had increased intakes of cholesterol over a period of years. Clinical evidence of coronary arteriosclerosis was considered to be coronary artery occlusion with myocardial infarction, angina pectoris, and certain conduction disturbances of the heart associated with arteriosclerosis. Electrocardiograms had been taken on 25 of the patients. There was definite evidence of coronary artery sclerosis in 9 per cent of the cases; 2 men and 1 woman had coronary occlusion with myocardial infarction, 3 men had angina pectoris, and 3 had either clinical or electrocardiographic evidence of arteriosclerotic heart disease or both. One patient died postoperatively either from coronary artery occlusion or from a pulmonary infarct; he was not included in the above 9 per cent. Five hundred patients, consecutively admitted to the hospital, in the same age period and with the same sex distribution, were used as a control group. None of these had been treated for peptic ulcer, none had any manifest endocrine disturbance, and all patients with arterial hypertension were excluded. Among these control subjects, the incidence of coronary artery sclerosis was 10.5 per cent; 3 per cent had a coronary artery occlusion, 2.5 per cent had angina pectoris, and 5 per cent had arteriosclerotic heart disease. The clinical evidence for this latter diagnosis was cardiac failure with an arteriosclerotic basis; electrocardiograms showed the conduction disorders associated with arteriosclerosis, evidence of a previous coronary occlusion, abnormal Q. R. S. complexes, or inverted T waves in Leads I, I and II, or I and IV. The rigidity of these criteria undoubtedly eliminated many patients who actually had atheromatous lesions in their coronary arteries, but avoided the inclusion of any who did not have these changes. Since the incidence of coronary artery disease was no greater in the patients treated for peptic ulcer with a diet that provided large amounts of cholesterol than in the controls, Shaffer concludes that "the nutritional role of cholesterol in the genesis of human atherosclerosis is of doubtful significance unless there is an associated endocrinopathy."

The limitations inherent in this type of study are self-evident. Plasma cholesterol determinations were not done and dietary data on the control patients were not provided. There is no proof, therefore, that a hypercholesteremia was present among the subjects treated for duodenal ulcer nor that the diet in the control group contained less cholesterol. These things are probable but the type of evidence presented is not likely to change the opinion of those investigators who believe that dietary cholesterol is etiologically important in the pathogenesis of atherosclerosis. The problem is obviously of tremendous importance in preventive medicine, and is deserving of even more vigorous study than has already been accorded it.

NUTRITION AND RHEUMATIC FEVER

Several attempts have been made to relate nutritional disorders to the pathogenesis of acute rheumatic fever. Rinehart, Connor, and Mettier (*J. Exp. Med.* **59,** *97 (1934)*), for instance, observed that the pathologic changes induced in guinea pigs by subjecting them to the simultaneous influence of vitamin C deficiency and streptococcic infection bear certain similarities to those seen in rheumatic fever. Subsequent studies showed that the plasma ascorbic acid level is almost uniformly low in patients with acute rheumatic fever, and is usually subnormal in persons convalescing from the disease (Rinehart, Greenberg, Olney, and Choy, *Arch. Int. Med.* **61,** *552 (1938)*). Other investigators have pointed out, however, that many infections have a similar effect on the amount of ascorbic acid in plasma, and have doubted that the pathologic lesions produced in the above experiments are characteristic of rheumatic fever. Furthermore, in clinical trials, the oral administration of vitamin C in considerable amounts has failed to prevent recurrences.

Coburn and Moore (*Am. J. Dis. Child.* **65,** *744 (1943)*), by studying the dietary habits of rheumatic children, a method that had been used several times before, have reapproached the problem. They point out that the incidence of acute rheumatic fever is higher in low income groups than among the well-to-do, higher in growing children than in adults, higher in urban than in rural communities. All of these factors tend to influence the nutritional status of the individual, and in each case the greater number of cases falls among those whose diet is least likely to be adequate. It should be stated parenthetically, however, that these same environmental influences may obviously be important also in determining degree or frequency of exposure to infections. The diets of 50 rheumatic children from families of low income were analyzed and compared with those of 50 nonrheumatic children from families on high income. Striking differences, which proved to be statistically significant, were observed. The most serious inadequacies were of protein, vitamin A, iron, and calcium. While only 2 of the normal children had diets deficient in vitamin A, 36 of the rheumatic subjects showed this dietary abnormality. In that half of the rheumatic group considered most susceptible to rheumatic fever, only 1 child received vitamin A in adequate amounts.

In spite of earlier clinical demonstrations that supplementary vitamin A does not seem to influence the occurrence of rheumatic manifestations, Shank, Coburn, Moore, and Hoagland (*J. Clin. Invest.* **23,** *289 (1944)*) have reinvestigated the relationship of vitamin A to the rheumatic state in a most thorough and methodical fashion. Levels of vitamin A and carotene in the plasma were determined on one group of 12 normal children from families in the high

income class and on three groups of rheumatic children classified respectively as having a vitamin A intake which was more than, equal to, or less than their theoretical requirements. Most of the subjects in the last group were on diets which provided only 56 per cent of the recommended daily intake. The average plasma values for the normal and the rheumatic groups with adequate or high vitamin A intakes were: for vitamin A, 108 to 139 I. U. per 100 ml.; for carotene 0.112 to 0.136 mg. per cent. The children with poor diets, on the other hand, had an average value of 93 I. U. per 100 ml. for vitamin A, and 0.084 mg. per cent for carotene. The plasma concentration of both substances, therefore, was lowest in the group with the smallest vitamin A intake.

Shank and associates next determined that the plasma vitamin A value fell appreciably in 9 children during periods of pharyngitis caused by beta hemolytic streptococci. With recovery, these values returned to normal. In 4 of the subjects who had a recurrence of rheumatic activity, however, there was a further fall in the concentration of the vitamin. The changes in plasma vitamin A and carotene were next followed in 57 children with active rheumatic fever. There was no significant change in the carotene levels, but the vitamin A concentration paralleled the severity of the disease, being lowest when the disease was most active and the sedimentation rate most rapid.

It was determined that no significant excretion of vitamin A occurred in the urine of rheumatic children even after a single large dose of the vitamin. A test dose of carotene in oil, representing 200,000 I.U. of vitamin A activity, given orally, caused slight increases in the plasma carotene level after twenty-four hours but did not significantly influence the plasma vitamin A in either normal or rheumatic children. It was not possible, therefore, to study the rate of conversion of carotene to vitamin A with this method. When 200,000 I.U. of vitamin A were given in one dose by mouth, there was a sharp increase in the plasma vitamin A concentrations, the peak values being reached in from five to eight hours. In 6 normal children, the maximum concentrations obtained varied from 1340 to 2400 I.U. per 100 ml. of plasma, whereas the corresponding values for 7 rheumatic children were only 274 to 1150 I.U. per 100 ml. These results indicate that in rheumatic fever there is either a decreased rate of absorption of vitamin A from the intestinal tract or an increased rate of removal from the plasma.

Patients with rheumatic fever, therefore, do show some abnormalities of vitamin A metabolism. As Shank and associates point out, however, similar changes have been observed in pneumonia and other acute infections, and even in artificially induced fever. It cannot be concluded that vitamin A deficiency is an important factor in the pathogenesis of rheumatic fever. Although nutritional studies have not yet suggested that any specific nutrient is of value in the practical problems of control and prevention of rheumatic fever, there remains the unchallenged observation that most children who develop the disease have generally inadequate diets. This fact will undoubtedly continue to challenge investigators until the pathogenesis of the disease is better understood.

DIETARY THIAMIN LEVELS AND DEFICIENCY SYMPTOMS

The somewhat arbitrary setting of optimal levels for vitamin requirements in man has raised a question in the minds of many as to the need for such high levels and, conversely, as to the level to which the intake of vitamins can be reduced without any harmful effects.

There are some who claim that the minimal levels are considerably below the figures recommended by the Food and Nutrition Board of the National Research Council. In support of this view are cited the many instances in which a less ideal diet is taken without observed harmful effects.

Rigid figures for these levels cannot be expected since conditions vary considerably and the body manifests various sorts of "margins of safety" and adaptations. The demonstration of thiamin synthesis in the bowel (Najjar and Holt, *J. Am. Med. Assn.* **123,** *683 (1943)*) illustrates a possible means of adaptation to unfavorable conditions of diet. However, it is desirable that data applicable to the majority of the population should be determined.

A number of investigators commenced studies several years ago with the purpose of gaining this information. One such study, started in 1940 and maintained under well controlled conditions, has now been reported by Foltz, Barborka, and Ivy (*Gastroenterology* **2,** *323 (1944)*). The subjects, 4 medical students, roomed and boarded in a hospital near the laboratory, and their only source of severe muscular exercise was work on an electrodynamic brake bicycle ergometer. Work tests were performed three times a week. The subjects worked at a rate of 1235 kilogrammeters per minute with a pedaling rate of 54 revolutions per minute. They did this until their "legs buckled." After ten minutes they started working at the same rate until their "legs buckled" again. Thus not only the work output of the two periods and the total work output could be measured, but the per cent of recovery could be calculated.

During the training period which lasted for nine to twelve months, an "adequate" diet approximating the recommendations of the Food and Nutrition Board of the National Research Council was given. The deficient diets were prepared, with one exception, to contain approximately the same and conventional proportions of carbohydrate, fat, and protein. The foods were selected to represent those commonly found in the American diet. The deficient diets were prepared so as to be deficient in thiamin and riboflavin by actual measurement. They were presumably deficient in other factors of the B-complex but data on these latter factors were not satisfactory. Under the "adequate" dietary regimen the subjects received a daily average of 1.44 mg. of thiamin and 2.67 mg. of riboflavin. The "deficient" diet contained 0.95 mg. of thiamin and 1.65 mg. of riboflavin. The "grossly deficient" diet contained 0.53 mg. of thiamin and 0.90 mg. of riboflavin. A similar diet but high in carbohydrate contained 0.61 mg. of thiamin and 0.62 mg. of riboflavin. Data are given for the ratio of thiamin to caloric intake. The latter ranged from 2500 calories in the smallest subject to 3200 calories in the largest subject.

Care was taken to avoid influencing the subjects psychologically when the diets were changed and in this the authors seem to have achieved success. Measurements were made, throughout the study, of the thiamin in the urine and in the blood and also of urinary riboflavin. Blood pyruvic acid determinations were also carried out.

A decreased appetite occurred within three weeks in all 4 subjects when the thiamin intake was reduced from 0.43-0.59 mg. per 1000 calories to 0.33–0.38 mg. At this time all the subjects complained of increased leg pains during and following the work periods and increased muscular tenderness of the legs. This was the outstanding complaint and the only complaint that appeared to increase uniformly in intensity until the deficient diets were supplemented with yeast.

Less than three weeks after the subjects were placed on the "grossly deficient" diet they became irritable and easily provoked. There was an increased desire for sleep, increased fatigue, and deterioration in mental attitude and alertness. On this "grossly deficient" diet the thiamin intake

had been reduced to between 0.17 and 0.12 mg. per 1000 calories. These subjective indications of deficiency as well as objective signs disappeared promptly after the addition of a yeast concentrate to the diet which yielded a total daily intake of 15.5 mg. of thiamin and 6.15 mg. of riboflavin.

In general the measurements of urinary thiamin and riboflavin paralleled the diet, although exceptions were observed. The urinary thiamin dropped to as low as 5 to 10 micrograms daily when the "grossly deficient" diet was taken, as compared with 80 to 320 micrograms under the "adequate" dietary regimen. Only one of the subjects at any time excreted less than 200 micrograms of riboflavin, a value which has been suggested as approaching the level of deficiency. The thiamin content of the whole blood was not well correlated with the urinary excretion of thiamin although it tended to correspond with the character of the diets. The blood pyruvic acid values remained normal at rest and after exercise and yielded no unequivocal information.

After reviewing the literature on the subject the authors conclude, on the basis of the literature as well as their own observations, that a daily dietary intake of approximately 0.20 mg. per 1000 calories of thiamin (a total daily intake of about 0.6 mg.) results in definite objective and subjective signs and symptoms of a dietary deficiency within eight weeks. They would place the minimum daily requirement for thiamin in young adult men at a range of from 0.33 to 0.45 mg. per 1000 calories. They point out that the experimental evidence on human subjects closely approximates the predicted deficiency level of 0.30 mg. per 1000 calories of Cowgill ("The Vitamins," *p. 173, ch. VIII, Am. Med. Assn. Chicago (1939)*). It was not considered that the low level of riboflavin was significant in producing symptoms or in influencing the results in the subjects.

The conclusions of Foltz and co-workers are at variance with those of Keys, Henschel, Mickelsen, and Brozek (*J. Nutrition* **26,** *399 (1943)*) who observed no deterioration in muscular or psychomotor performance of 4 young men kept on an intake of thiamin of 0.23 mg. per 1000 calories (total 0.7 mg.) in the presence of "adequate" riboflavin and nicotinic acid. It is unfortunate, from the standpoint of conclusions relating to thiamin alone, that the diet of the subjects of the experiment of Foltz, Barborka, and Ivy was deficient in more factors than thiamin alone.

HISTIDINE DEFICIENCY IN MAN

The amino acid histidine has been found to be a growth essential in the rat (Rose and Cox, *J. Biol. Chem.* **61,** *747 (1924)*), but it has not been proved that it is required for the maintenance of the adult rat. Burroughs, Burroughs, and Mitchell (*J. Nutrition* **19,** *363 (1940)*) have reported that the rat can be maintained in nitrogen equilibrium in spite of the absence of this amino acid in the diet, and similar data on adult human subjects have recently been obtained by Rose and co-workers and confirmed by Holt *et al.*

Albanese, Holt, Frankston, and Irby (*Bull. Johns Hopkins Hosp.* **74,** *251 (1944)*) report a study of the human requirement for histidine. The method employed was to feed 3 normal adult males an experimental diet consisting of fats, starches, and certain fruits and vegetables of low protein content. These provided approximately 10 per cent of the daily nitrogen intake. The remaining 90 per cent was supplied as a histidine-deficient casein digest. Almost complete removal of histidine from this casein digest was shown by analysis. l-Tryptophane and l-cystine were added to the casein digest. The caloric intake

was maintained at 38 to 43 calories per kilogram per day and the nitrogen intake at 0.1 g. per kilogram per day.

The subjects were given a low protein diet for two days before the start of the experiment in order to expedite the attainment of nitrogen equilibrium. This was followed by a control period of six days during which the histidine-deficient diet was supplemented with l (+) histidine hydrochloride. There followed a thirty-six day period on the deficient diet, after which histidine was given as a supplement in increasing amounts for periods of three days each.

None of the 3 subjects developed clinical symptoms, nor were any definite changes noted in their blood chemistry or morphology. The nitrogen balances remained positive throughout and the excretion of histidine in the urine showed no reduction. Nevertheless, all lost weight during the course of the experiment.

The "indican" output in the urine was measured by the Sharlit adaptation (*J. Biol. Chem.* **99,** *537 (1932)*) of the Jolles reaction. In all of the subjects an increased "indican" reaction was noted. Furthermore, the color of the test was emerald green rather than lavender. This reaction had not been found in subjects on parallel experiments in which other amino acid deficiencies were induced. Furthermore, when one of the subjects was given l-histidine in substantial amount (1.5 per cent), the value for the "indican" excretion fell promptly and the green color was replaced by lavender. In another subject receiving only a third of this amount of histidine as a supplement, the drop in the "indican" value was less marked and the color changed from pure green to a purplish green. In these 2 subjects only a partial reversion to normal occurred in the control period following the deficiency whereas in the third subject in whom the experiment had not been temporarily interrupted, the feeding of 1.5 per cent histidine in the postcontrol period produced a return to a normal "indican" value and the usual lavender color.

These studies prove that histidine is not an essential for the maintenance of nitrogen equilibrium in the adult, and are in keeping with the findings of Rose, Haines, Johnson, and Warner (*J. Biol. Chem.* **148,** *457 (1943)*). They do suggest however that histidine may be essential for certain metabolic phenomena other than the maintenance of nitrogen equilibrium. Albanese and associates cite the weight loss which was observed, although they admit that they were unable to prove that this loss of weight might not have been due to inadequate calories. They appreciate the possibility that the abnormal metabolite, observed by them in the urine during the histidine-deficient period, may represent a by-product of some synthetic reaction by which histidine is formed. At the same time they point out that this metabolite may be an indication of a process of tissue destruction which does not result in a negative nitrogen balance. It is possible that a histidine-deficient diet may result in atrophic changes in some essential tissue which represents such a small fraction of the body that its disintegration is not detected in a nitrogen balance study. This possibility cannot be denied and consequently further observations will be followed with great interest.

SERUM PHOSPHATASE ACTIVITY AND RICKETS

Klasmer (*Am. J. Dis. Child.* **67,** *348 (1944)*) reports a study in Jerusalem of serum phosphatase activity in 1000 unselected children ranging in age from 6 months to 2½ years. After pointing out that the normal values for phosphatase activity in children have not been established with accuracy, determinations are recorded

on 320 healthy children between 6 months and 2½ years of age. The mean value was 9.409 units ± 2.796 with a range of 5.59 to 15.0 units as represented by two standard deviations. The measurements were made by Rappaport's modification ("Mikrochemie des Blutes," *Akademische Verlags- und Versandbuchhandlung Emil Haim & Co. p. 175, Vienna (1934)* of Bodansky's procedure (*J. Biol. Chem.* **101,** *93 (1933)*).

There were 88 instances in which the serum phosphatase activity was greater than 15 units. The phosphatase activity was found to be well correlated with signs of active rickets and there was a pronounced parallelism between severity of symptoms and increase of phosphatase activity. Fifty-five of the 1000 children examined were found clinically to have active rickets as indicated by craniotabes, rachitic rosary, and unequivocal swelling of the epiphyses. An increase in the phosphatase activity was found in 3 cases where rickets was probably not the cause. With these occasional exceptions, however, the data indicated that phosphatase activity is a valuable and probably the most sensitive index of active rickets, while skeletal deformities are also a useful index.

There has been considerable divergence of opinion as to the prevalence of rickets in the countries of the Near East and the incidence has been reported to range from 6 to 60 per cent. Obviously one reason for this difference in findings is the variation in the criteria and definition of the diagnosis. According to Klasmer's findings the incidence of active rickets in Jerusalem in children at a welfare center was possibly as great as 8.8 per cent.

Klasmer noted a significant variation in phosphatase activity in relation to the seasons, a sudden rise occurring in winter and a drop commencing in the spring which reached its lowest level in the autumn. The greater intensity of ultraviolet irradiation in Jerusalem as compared with Prague and Arosa was indicated by the lower levels obtained at all seasons, even at the peak of winter in the Near East. It is interesting that even in "normal" children a seasonal variation similar to that found in children with poor development was observed.

PROTEIN REQUIREMENT IN HOT ENVIRONMENTS

The protein requirement of men doing hard physical work has been estimated by many authorities, and the values range all the way from 50 g. per day (Chittenden) to 165 g. per day (Rubner). The value currently recommended by the National Research Council is 70 g. per day. These suggestions have all been based on observations made in temperate environments. What effect, if any, a higher temperature might have on the protein demands of the body remained an open question. The uncertainty lay in a curious discrepancy between the preferences of men accustomed to work in the heat and the deductions of an older school of physiologists. Rubner and Lusk both recommended a reduced protein intake for men working in hot environments. Their conclusion was based on the ground that the high specific dynamic action of protein imposes an unnecessary load upon the heat dissipating mechanisms of the body already taxed by the hot environment. Nevertheless, men like farm laborers, threshers, baseball players, and miners are known to prefer a diet containing liberal quantities of meat, and one might suppose that any deleterious effect of protein should have been noted in the course of this ordinary experience.

Pitts, Consolazio, and Johnson (*J. Nutrition* **27,** *497 (1944)*) have fed diets high or low in protein to 3 healthy young men and then measured the physical fitness of the

subjects for hard work in a temperate environment and under conditions simulating the climate of the tropics or of the desert. The temperate environment was standardized at 75°F., 50 per cent relative humidity and zero wind, and the subjects ran a motor-driven treadmill at 7 miles per hour up an 8.6 per cent grade for five minutes or until exhausted. At the higher temperatures experiments involving such severe exercise proved to be impractical. Hence easier but more prolonged exercise (marching) was imposed. The grade was 2.5 per cent, the speed 3.5 miles per hour, and the time one hour and twenty minutes. Moist tropical conditions were standardized at 95°F., 85 per cent relative humidity, and a wind of five miles per hour. Desert conditions were established at 110°F. and 25 per cent humidity. The subjects spent ten to twelve hours a week in the heated room, and their intakes of salt and water were adequate at all times.

The subjects ate in a college dining hall. For the first two months the customary normal diet contained an average of 3040 calories and 105 g. of protein per day. This was followed by a six week period during which 3970 calories and 149 g. of protein were consumed in a typical day. During the following six week period the intake of protein was reduced to 76 g. per day with a corresponding increase in carbohydrate. This so-called "low-protein diet" therefore contained approximately the amount of protein recommended by the National Research Council. The original "normal" diet was ingested during the final period.

Physical fitness was scored arbitrarily on the basis of duration of effort and the sum of three pulse measurements taken at regular intervals. Measurements were also made of the respiratory exchange at rest, while standing, and after reaching a steady state during the marches. Urinary nitrogen and plasma protein were also determined.

Plasma protein and body weight tended to be highest while the high protein diet was being ingested, although the variations due to diet were not large. Urinary nitrogen, as might be expected, varied with the intake of protein. Within the ranges studied, the variations in the amount of protein consumed (76 to 150 g. per day) did not exert any marked effect on physical fitness. In fact as the experiment progressed, there was a continued improvement with training which was more noticeable than the effect of diet. Performance was better during the second period (high protein) than on the original normal diet; it was still better during the subsequent period when the low protein diet was fed, and it remained unchanged when the subjects consumed the original normal diet. Pitts, Consolazio, and Johnson point out that their results are very similar to those of Chittenden (1904) who, however, attributed the observed improvement to the low protein diet.

The ability to withstand the high temperature, likewise, did not appear to be altered by variations in protein intake within the ranges of 75 to 150 g. per day. Again there was improvement associated with training and acclimatization. But even in environments which were extremely severe the subjects performed at least as well on the high protein diet as on the others. It is concluded that the heat dissipating mechanisms of the body are so efficient that the effect of a high protein diet is virtually insignificant. The effect of a diet very low in protein still remains to be determined.

DEFICIENCY ANEMIA IN INFANTS

There is an increasing awareness of the importance of nutritional factors in the causation of anemia. This is true particularly in regard to anemia occurring in

infants. Anemias in infancy have long been confusing and are badly in need of systematic and comprehensive investigation.

Bass (*Am. J. Dis. Child.* **67,** *341 (1944)*) reports 2 cases of anemia in infants which he regards as nutritional in origin. The first patient was a prematurely born infant who at 6 months of age was found to have a severe anemia with the red cell count below 1 million cells per cubic millimeter. She had had a nasal and pulmonary infection. Repeated transfusions produced no striking benefit and consequently intramuscular injections of liver were given. The changes in the red cell count which followed are interpreted as indicating that this infant was deficient in the antipernicious anemia principle. Within one week the content of hemoglobin in the blood rose to 60 from 38 per cent and the red cell count to 3.18 million from 1.96 million.

A clearcut response to liver extract therapy in an infant is so unusual that it is unfortunate that the data presented are not more adequate. It is stated that the proportion of reticulocytes rose from 2 per cent to 16 per cent after liver therapy was started. The details of this, however, are not given. It would be desirable to know whether this rise in reticulocytes was a consistent and regular one such as occurs in pernicious anemia. One is also left in a somewhat doubtful state of mind since the extraordinarily low blood count previously mentioned was followed on the next day by a count of 2.6 million and 54 per cent hemoglobin. If a rise to this level can occur from 0.92 million and 17 per cent hemoglobin in one day, the significance of the later variations seems doubtful.

In the second case, anemia was observed in a child who was receiving goat's milk. This had been substituted for cow's milk because of apparent sensitivity to the latter. Goat's milk anemia has been described as being very similar to that seen in pernicious anemia in adults. It has been claimed that the anemia may be cured by giving liver or yeast extract (Rominger, Meyer, and Bomskov, *Ztschr. f. d. ges. exp. Med.* **89,** *786 (1933)*; György, *Ztschr. f. Kinderh.* **56,** *1 (1934)*). American workers have heretofore not been able to confirm the European observations, but Orten and Smith (*Yale J. Biol. Med.* **8,** *637 (1936)*) suggest that this difference in results is due to the difference in the nutritive content of goat's milk in Europe and in this country.

In the case reported by Bass, severe anemia was noted. This failed to respond to long continued treatment with large doses of iron and vitamins or following several transfusions. Because of its poorly nourished condition the infant's diet was changed to one containing a hydrolysate of casein supplemented with yeast and dextrimaltose. The child improved greatly, but again the evidence that the therapy directly influenced the blood picture is not very convincing. It depends on the observation that "the hemoglobin content and red cell count did not drop, as they had done previously, after the effect of the transfusions had worn off."

While the questions which Bass raises are of considerable interest, it is unfortunate that he has not furnished better evidence in attempting to answer them.

VITAMIN B-COMPLEX AND HARD WORK

Even in ordinary times one would expect public interest in the question of whether a high intake of vitamins is necessary for the performance of hard physical work; in time of war the problem of an adequate diet for the soldier is so obviously important that much research on the subject has resulted. The general character of these experiments

has been indicated in previous reviews in this journal (*Nutrition Reviews* **1,** *227 (1943)*; **2,** *115 (1944)*).

Human subjects are fed an ordinary diet and made to perform set exercises, and arbitrary measurements of physical fitness are applied. The diet is then altered either by reducing the content of some essential (vitamin or protein) or by the additional consumption of vitamin pills or placebos. The same tasks and measurements are then applied. The experiments have indicated rather clearly that no great benefit results from the consumption of high amounts of vitamins in addition to a good diet such as this army post ration was (Keys and Henschel, *J. Nutrition* **23,** *259 (1942)*). The effects of a moderate reduction in vitamin intake have not been established with certainty, although several groups of workers have reported decreased physical efficiency on diets considerably below the recommendations of the National Research Council, particularly with regard to thiamin and riboflavin.

Keys *et al.* (*J. Nutrition* **27,** *485 (1944)*) in a recent publication on the subject report a study on 8 normal young men who were maintained on a highly restricted basal diet consisting of such materials as macaroni, polished rice, bread, butter, jelly, and a special cream made by diluting a preparation of 70 per cent butterfat. Small amounts of canned fruits were provided. All flours and cereals were low vitamin preparations, and only flavoring amounts of chicken, beef, or veal were allowed. The daily average protein intake on this diet was 85 g., and roughly 35 per cent of the calories were provided as fat. Supplements of minerals and the fat soluble vitamins were furnished in the amounts recommended by the National Research Council.

The vitamins of the B-complex were supplied in special capsules. During the first twenty-one days all subjects received the amounts recommended by the National Research Council. For the next fourteen days only the deficient basal diet was fed. This supplied 0.16 mg. of thiamin per 1000 calories, 0.15 mg. of riboflavin, and 1.8 mg. of niacin. Five of the subjects received placebos; 3 received abundant B-vitamins. Neither the subjects nor the observers knew which they were receiving. During a final period all subjects again received adequate B-vitamins.

The subjects performed fixed tasks, most of them on treadmills, involving a daily expenditure of 4500 to 5000 calories. Extensive series of physiologic, biochemical, and psychologic tests were made at intervals. These included measurements of endurance, anaerobic work, speed, coordination, and muscular strength, and questionnaires were filled out periodically. Chemical studies were made of the blood and urine. As might be expected the vitamin content of the urine was found to vary with the vitamin intake of the subjects. All other tests, however, failed to show any correlation whatever with vitamin intake; in other words, there was no evidence of physical or psychologic deterioration after fourteen days of hard work on a diet very low in the vitamin B-complex. This result is diametrically opposite to that reported previously by Johnson *et al.* and reviewed in this journal (*Nutrition Reviews* **1,** *227 (1943)*). In discussing this discrepancy, Keys *et al.* describe the earlier Harvard experiment as follows: "A group of sedentary laboratory workers, highly conditioned to expect marked effects, were suddenly put to unaccustomed severe physical work and were fed a peculiar and monotonous diet. Apparently they all suffered in differing degrees from the symptoms which have been widely publicized for thiamin deficiency.... The subjective symptoms... were of the vague type commonly related by the neurotic patient and easily induced by suggestion."

Johnson, Darling, and Forbes have replied that "the completeness and thoroughness of Dr. Keys' work leave no

doubt about the reliability of the results," but his interpretation of their own work is rejected. Both groups of results are regarded as real and valid. The Harvard experiments were controlled by placebos much as the Minnesota experiments; the Harvard subjects were in good physical condition and most of them had just completed experiments involving rigorous physical training. Far from being conditioned to expect results, none of the subjects really expected any change in the short time allowed for the experiment. No deficiency symptoms appeared on either earlier or later field trips when the diet was adequate. The apparent discrepancies in results are therefore attributed to the differences in the experimental conditions employed. The Minnesota subjects lived in a temperate laboratory environment; the Harvard group worked outdoors in winter. The Minnesota subjects exercised on a treadmill; the Harvard group performed various outdoor activities. Finally, and probably most important, the daily intake of thiamin was lower in the Harvard subjects who showed signs of deterioration, than in the Minnesota subjects who did not.

Two facts emerge from these experiments. Those of Keys *et al.* indicate that for at least a few weeks a normal man can perform severe physical work on a relatively poor diet without evidence of harm. The experience of Johnson *et al.* indicates that more work needs to be done to establish the limits of abuse, dietary and otherwise, that man can tolerate.

NUTRITIONAL QUALITY OF PROCESSED FOODS

As methods of agricultural mass production and the trend toward a large urban population have developed, the time interval between production and consumption of foods has increased tremendously, and the effects of the methods used to preserve the food during this interval on its nutritive properties have become of increasing practical importance. Food technologists have amassed a great deal of detailed data on the effects of different methods of preservation on the content of various nutritional essentials, but since the types of foods which are processed and the methods of processing do not remain static, new information is constantly needed.

Because of the contribution which meat makes to the diet, particularly with respect to proteins and the vitamin B-complex, studies of the values of these nutrients in canned and dehydrated meat and meat products (Rice and Robinson, *Am. J. Pub. Health* **34,** *587 (1944)*) have particular significance. Previous work in the same laboratory (Poling, Schultz, and Robinson, *J. Nutrition* **27,** *23 (1944)*) has indicated that the biologic value of the proteins of canned pork and of dehydrated pork and beef was not significantly below that of the raw meats when fed at a level of 18 per cent protein in the diet.

The vitamin content of the meat was then determined from representative samples of meat at various stages in the processing operations and after storage under known conditions for varying lengths of time. The assays for thiamin were made by the thiochrome method; those for riboflavin, niacin, and pantothenic acid by microbiologic methods after enzymatic digestion.

There was excellent retention of these vitamins in dehydrated pork and beef, with losses closely approximating those found in cooking by home methods. The per cent retention for thiamin and pantothenic acid in the dehydrated products ranged from 63 to 76 per cent, and was consistently above 90 per cent for riboflavin and niacin.

The loss of thiamin in cured pork during canning was found to be dependent on the duration of heat processing and thus indirectly related to the size of the cans. Six

pound cans, which required over three hours at 235°F. for processing, retained only 43 per cent of their original thiamin content, as compared with 67 per cent retention in 12 ounce cans which were processed for little more than an hour at 232°F. Except for thiamin, there was no apparent difference in the vitamin retention in the two sizes of containers. Again, 90 per cent or more of the niacin and riboflavin content was retained, and 76 per cent of the pantothenic acid.

To determine the effects of storage, replicate vacuum-packed samples of canned cured pork, dehydrated pork, and dehydrated beef were stored at six constant temperatures ranging from −20° to 145°F., and samples removed for assay at intervals varying from twenty-eight to two hundred ninety-three days. In canned pork there was excellent retention of all vitamins at temperatures to which the product would ordinarily be subjected. There was only a 7 per cent loss of thiamin after ten months storage at 38°F., and 52 per cent of the original thiamin content was retained after ten months at 80°F. At higher temperatures the loss of thiamin was much more rapid, much of the vitamin disappearing after only four weeks at temperatures of 120° and 145°F. Up to and including 99°F. there was little if any loss of riboflavin, niacin, or pantothenic acid after ten months storage. At higher temperatures about 30 per cent of the riboflavin and pantothenic acid were lost. In the dehydrated pork, thiamin appeared to be less stable than in the canned product, with losses of 50 per cent after two months storage at 80°F. However, at −20° and 38°F., losses of thiamin were negligible. The behavior of the other vitamins in the dehydrated pork followed closely the losses observed in the canned product. With dehydrated beef, 100 per cent retention of niacin, riboflavin, and pantothenic acid was obtained after two hundred nineteen days storage at 99°F. There was no evidence of better retention of thiamin in dehydrated beef than in dehydrated pork.

So it appears that although commercial processing methods differ greatly from those of household cookery, the loss of vitamins by both methods is practically the same if the vitamin content of the cooking juices is included with that of the cooked meats. In general, the vitamins lost and the degree of their loss in the processing of meat is similar to the changes induced by processing of other foods, such as the baking of bread and the dehydration of vegetables.

Feaster (*Am. J. Pub. Health* **34**, *593 (1944)*) discusses in somewhat more general terms the effect of processing on the nutritive value of canned fruits and vegetables. It is pointed out that, in view of the wide variation in content of the freshly harvested foodstuffs in dietary essentials, the nutritive quality of the fresh material is probably as important a factor in determining the content of the finished product as what happens to it during processing. The chief nutritive values of these foods are associated with their vitamin and mineral content, although the carbohydrate of fruits packaged in heavy syrup and the protein of legume vegetables may make substantial contributions to the diet. The influence of canning on the mineral nutrient is confined to mechanical separations, leaching effects, or possible changes in availability. The provitamins A contained in canned leafy green and yellow vegetables may constitute a major dietary source of vitamin A. Aside from mechanical removal of certain tissues during preparatory operations and the susceptibility to oxidation after maceration of vegetables under conditions where enzyme activity is not inhibited, the provitamins A appear to be well retained in the canning process. Canned citrus fruits and tomato products often constitute the most important dietary source of ascorbic acid, and, while the more concentrated sources of the B-vitamins are not found among fruits and vegetables, the canned products can contribute an important fraction of the total intake of thiamin, niacin, and riboflavin. It is these water soluble

vitamins which are more likely to be sacrificed in the canning process, all of them by leaching, thiamin because of its heat labile nature, and ascorbic acid because of the ease with which it is oxidized.

The preparation and commercial canning of fruits and vegetables is considered in three general patterns according to the material being handled. The handling of acid products with a pH under 4.5, chiefly fruits, in large discrete particles, involves the removal of undesirable or inedible portions and often the addition of sugars—procedures comparable to home preparation of fruits for serving. The large size of the pieces tends to limit the effect of leaching of water soluble materials. Partial exhaustion or displacement of oxygen from the can headspace before sterilization minimizes the oxidation of ascorbic acid, and the thermal stability of thiamin at a pH more acid than 4.5 is such that little loss of this vitamin is entailed. Laboratory data indicating negligible changes in ascorbic acid and thiamin content of tomatoes during canning support this generalization.

In preparing juices the procedure is roughly similar, except that a definite loss of provitamin A may occur in case the pulp of the fruit is not included in the juice. The retention of ascorbic acid in canned tomato juice or citrus fruit juices is dependent on the degree of protection from atmospheric oxygen during extraction and subsequent operations, and under good commercial conditions the loss is negligible. Heat in itself appears to be an unimportant factor when precautions are taken to exclude oxygen.

The third general pattern, used for products with a pH above 4.5, chiefly vegetables, as discrete particles, introduces a preheating treatment known as a blanch or a scald in order to cleanse and shrink the products, expel gases, and inactivate enzymes. Losses of water soluble nutrients up to as high as 25 per cent may result from the leaching effects of this step; a portion may pass into the liquor in which the vegetables are packed. Some data are presented which indicate that the loss of ascorbic acid in commercial canning of vegetables is much less than would be anticipated from the relatively severe heat treatment necessary to effect sterilization, with retention in peas and green beans of 90 per cent or more of their content prior to processing. Thiamin losses of 40 per cent for peas and 20 per cent for green beans during heat treatment are reported. Losses will apparently vary according to many factors, including season, type, and maturity of product, and exact method of processing used. Further losses may of course occur in storage, with temperature at which the canned goods are stored being an important factor. The mechanism of these and concomitant changes in flavor and often color in stored processed foods remains little understood and is a basic research problem in this field.

DIETARY FACTORS THAT INFLUENCE CARCINOGENESIS

It has become apparent that the nature of the diet can be of considerable influence on the production and development of experimental tumors. Various specific instances of relationships between diet and tumors have been previously reviewed (*Nutrition Reviews* **1,** *51, 144, 174, 216, 247, 271, 361 (1942-43)*; **2,** *79 (1944)*). Rusch (*Physiol. Rev.* **24,** *177 (1944)*) has reviewed the "Extrinsic Factors That Influence Carcinogenesis," and a prominent position has been given to the influence of dietary factors. There appears to be an advantage in considering all of the dietary factors at one time, since by so doing certain general principles tend to emerge.

In a number of experimental tumors, four distinct dietary influences have been demonstrated: (1) caloric intake, (2) fat consump-

tion, (3) protein or amino acid composition of the diet, and (4) deficiency of certain of the vitamins.

Repeated observations show that mere restriction of food consumption decreases both the growth rate and the incidence of tumors. This is true of spontaneous as well as artificially induced tumors. There is perhaps more influence on the incidence of tumor formation than on subsequent growth of the neoplasm. A moderate caloric reduction will reduce tumor incidence, it requires a drastic decrease in food intake to retard the development of tumors already established, and this retardation is not demonstrable for all tumors. The decreased incidence of tumor production is frequently striking, e.g. the incidence of spontaneous breast carcinomas in a cancer strain of mice was reduced from 67 per cent to zero by decreasing the caloric intake (Visscher, Ball, Barnes, and Sivertsen, *Surgery* **11,** *48 (1942)*). Although one would not anticipate such clearcut evidence in man, Tannenbaum (*Arch. Path.* **30,** *509 (1940)*) has collected data from life insurance statistics suggesting that cancer mortality increases with increasing body weight.

Increasing the fat content of the diet increases the incidence of certain tumors, especially in skin tumors induced by carcinogenic hydrocarbons. There appear to be at least three factors involved. First, there is a local effect resulting from the fat which the experimental animals (mice) smear on the skin from the fatty diet. For this reason, fat administered in the drinking water, as an emulsion, is only about half as effective as that given in the food cup. Presumably the fat on the skin augments the absorption of the carcinogen, or in some other manner enhances its action. A second factor seems to be the increased caloric consumption of animals on a moderately fat diet. A third factor must be a specific effect of the fat itself, since the incidence of spontaneous mammary carcinoma in mice is increased by high fat diets as compared to controls on a low fat diet but with an equal caloric consumption. In this case both local and caloric influences would appear to be ruled out.

Fat, however, by no means stimulates all tumors. Many types either are not influenced by the fat content of the diet or may actually be inhibited by at least certain types of fat. For example, hepatoma formation resulting from butter yellow administration had an incidence of about 60 per cent when 5 per cent corn oil was included in the diet, whereas substitution of 5 per cent of hydrogenated coconut oil lowered the incidence to 8 per cent or less (Miller, Kline, Rusch, and Baumann, *Cancer Research* **4,** *153 (1944)*). It is not clear whether the hydrogenated oil contained substances inhibitory to tumor formation, or whether the corn oil contained stimulating materials. Many other fatty substances have been tested for their influence on tumors without definite rational results. Efforts have been made to implicate cholesterol in tumor formation but with little success. One report indicates that lecithin increases the incidence of induced hepatomas.

The incidence of a number of tumors, both spontaneous and artificially induced, is lessened by decreasing the cystine content of the diet. This is usually accomplished by restriction of the casein level in the diet, since cystine is the limiting essential amino acid in casein. One wonders whether this is not another example of the influence of reduction of caloric intake, or at least of an analogous phenomenon. It is conceivable that restriction of other essential amino acids might have the same result. Curiously enough, in induced hepatomas, if the casein or cystine intake is increased to generous levels, the tumor incidence decreases again, providing the diet is complete in other respects, i.e., there is a maximal tumor incidence at intermediate cystine levels.

Deficiencies of certain vitamins influence tumor incidence. Riboflavin deficiency has been shown to increase the incidence of induced hepatomas in rats. In contrast, deficiency of either biotin or pyridoxine decreases the incidence of this tumor. In addition,

pyridoxine deficiency has been shown to decrease the incidence of several other tumors. In at least one instance, the influence of caloric intake was ruled out.

In order to explain the various dietary influences on tumors, it seems to be necessary to consider both the metabolism of the normal and the tumor cells. The cells of the liver, for example, seem to be rendered more sensitive to toxic substances by an incomplete diet. When the toxic substance is a carcinogen, an incomplete diet might be expected to lead to an increased tumor incidence provided the missing dietary substance, riboflavin for example, is more essential to the normal liver cell than to the tumor cell, or conversely, to a decreased tumor incidence in case the missing substance is more essential to the tumor cell than to the normal cell, e.g. pyridoxine or biotin.

The inhibitory influence of low caloric intake on tumor production results, one suspects, from an altered response of the normal cell to carcinogenic agents. Perhaps the rate of cell division is not augmented to as great an extent in the face of a caloric shortage, and it would appear that an augmented mitotic rate is important for conversion of normal to tumor cells.

In addition to the establishment of the above well defined dietary influences, considerable effort has gone into testing particular foodstuffs or tissue extracts for their influence on various types of tumors. Many of the results obtained appear to be explainable on the basis of correcting or inducing deficiencies of calories, proteins, or vitamins. One gains the impression that apparent confusion arises from differences in control diets. For example, with a control diet very low in cystine, addition of a cystine-containing foodstuff would be expected to increase the incidence of induced hepatomas. On the other hand, if the control diet contained a moderate amount of cystine and was otherwise well balanced, the addition of cystine-containing material would be expected to decrease the incidence of this same tumor.

That so much success has attended the study of dietary influences on experimental tumor formation suggests that further intensive work along these lines would be highly profitable. It is too early to tell whether it will be possible materially to influence human tumor incidence or development through the dietary regimen, but such an eventuality does not seem to be excluded by the results already obtained with experimental animals.

METHIONINE AND LIVER NECROSIS IN MAN

Some twenty years ago it was claimed that carbohydrates exert a protective action on the liver, and great emphasis was laid on administration of large amounts of glucose to patients suffering from all types of hepatitis. During the past five years, however, it has become clear from experience gained from animal experiments as well as from clinical observations that the protective effect of proteins against liver injuries is of far greater importance than that rendered by carbohydrates. Thus Miller and Whipple (*Am. J. Med. Sci.* **199,** *204 (1940)*) found that protein deficiency rendered the liver of dogs more susceptible to chloroform necrosis, and Hock and Fink (*Z. physiol. Chem.* **279,** *187 (1943)*) describe the development of liver necrosis in young rats on yeast protein diet due to the lack of cystine in yeast protein. The same authors found that extra addition of cystine to the yeast diet protected the animals against the liver necrosis. Likewise rats fed a synthetic diet containing 10 per cent of casein or less developed liver injuries which could be prevented by the addition of methionine to the diet (György and Goldblatt, *J. Exp. Med.* **75,** *355 (1942)*; Webster, *J. Clin. Invest.* **20,** *440 (1941)*; Blumberg and McCollum, *Science* **93,** *598 (1941)*; Lillie, Daft, and Sebrell, *Pub. Health Reports* **56,** *1255 (1941)*).

The importance of the sulfur amino acids for the normal function of the liver appears also from the studies of Miller and Whipple (*J. Exp. Med.* **76,** *421 (1942)*), who report that methionine is the most effective factor in the protection of the livers of protein depleted dogs against chloroform poisoning. Further reports dealing with the protection of the liver by methionine have appeared in recent years. Himsworth and Glynn (*Lancet* **I,** *457 (1944)*) report that liver necrosis developed in rats on low-protein diet is prevented by methionine, and Goodell, Hanson, and Hawkins (*J. Exp. Med.* **79,** *625 (1944)*) find that liver necrosis in protein depleted dogs injected with the toxic drug mapharsen, is partially prevented by feeding methionine. In protein depleted dogs doses of 2 to 2.5 mg. per kilogram cause liver injury with jaundice, whereas dogs to which methionine was administered by mouth twenty to twenty-four hours prior to the injection will tolerate 4.5 mg. mapharsen per kilogram without any icterus developing. There seems therefore to be abundant evidence from animal experiments that the sulfur-containing amino acids, and particularly methionine, aid in protecting the liver against numerous toxic agents.

Clinical studies of the relation between liver diseases and the intake of protein, though yet preliminary, tend to substantiate the animal experiments. Beattie and Marshall (*Nature* **153,** *525 (1944)*) have published a preliminary report of their investigations of the effect of certain of the amino acids on various liver diseases in man. The authors were particularly interested in "(a) the prevention of liver damage during arsenical treatment for syphilis; (b) the treatment of established liver damage in cases of infective hepatitis and 'post-arsphenamine' jaundice; and (c) the treatment of patients gravely ill with liver dysfunction extending over a period of many weeks or months."

The observations of Beattie and Marshall indicate that occurrence of liver damage during arsenical treatment can be either prevented or minimized by the administration of methionine, or by the use of casein digests (which are known to be rich in methionine) supplemented with extra addition of cystine. The preliminary results were based on a study of 450 cases of hepatitis (infective and post-arsphenamic) including controls; and although the results have not yet been treated statistically, the authors feel justified in drawing the following conclusions: "that the clinical course of the above diseases is influenced beneficially, and the period in hospital significantly shortened, by treatment either with pure methionine in properly regulated dosage or by feeding patients with rapidly absorbable casein digests rich in methionine. In gravely ill patients, the results obtained by methionine treatment have been so striking as to leave no doubt as to the efficiency of the treatment, especially in those cases which have remained jaundiced for weeks or months and were in a state of *icterus gravis* when methionine treatment was initiated." The group of patients observed by the authors includes mainly toxic liver diseases.

Himsworth and Glynn divide the causes of liver necrosis into a toxic group—toxipathic hepatitis, and a dietetic—trophopathic hepatitis. The toxipathic and trophopathic hepatitis frequently occur mixed.

A pure trophopathic hepatitis occurs infrequently in man. However, Himsworth and Glynn refer to the occurrence of liver cirrhosis observed among the poor natives of Punjab which has been ascribed to a deficiency of protein in the diet. As a support for this suggestion, Gillman (*Brit. Med. J.* **1,** *149 (1944)*) has found that rats fed a diet habitually eaten by the affected natives developed cirrhosis of the liver.

In an analysis of a large number of patients with Laennec's cirrhosis of the liver, Ratnoff and Patek (*Medicine* **21,** *207 (1942)*) found that besides alcoholism, dietary factors were of importance in the development of the disease.

Typical toxipathic liver diseases are the more or less malignant cases of hepatitis due to inhalation of trinitrotoluene and chloro-

form. The great practical importance of preventing trinitrotoluene intoxication, which now occurs frequently in war factories, is obvious. Chloroform, on the other hand, has largely been abandoned as an anesthetic. However, a modern anesthetic "trilene," used for induction before ether anesthesia, has been reported to give rise to liver necrosis. Report of a case of fatal liver necrosis on a girl of 2 years of age and reference to other fatal cases of trilene hepatitis is to be found under "Annotations" (*Lancet* **I,** *476 (1944)*).

Rae and Wilkinson (*Lancet* **I,** *332 (1944)*) have reported that tannic acid used as a dressing for burns decidedly impairs the liver function, as judged by the levulose-tolerance test. These workers found that impairment of liver function was much less pronounced in the group of patients treated with gentian violet and silver nitrate, although the burns in this group were much larger than those treated with tannic acid jelly.

The liver damage produced by arsphenamine seems, as already pointed out, to depend very much on the nutritional status of the organism.

The infectious hepatitis may be a mixed toxipathic and trophopathic liver disease. It has been reported that general malnutrition gives rise to an increased incidence of hepatitis (Strümpell, *Deutsche med. Wchnschr.* **47,** *1219 (1921)*).

The aggravation of infectious hepatitis in pregnant or lactating women furnishes the most striking example of the effect of protein depletion on hepatitis in man. Himsworth and Glynn in their review quote some old French clinicians who have reported several cases where an otherwise mild epidemic of hepatitis gave rise to fatal liver necrosis in pregnant women. Thus the malignant liver necrosis which occurs in pregnancy is to be regarded as "a conditioned deficiency disease."

A prevention of the dreadful liver necrosis in pregnancy by extra addition of methionine would certainly constitute one of the most noteworthy advances in modern medicine. However, further clinical data are necessary before any final conclusions can be drawn regarding the applicability of methionine in hepatitis in man.

VITAMIN PILLS FOR INDUSTRIAL WORKERS

The two opposing schools of thought on the advisability of supplementing workers' diets with vitamin pills have been aptly summarized by Cowgill (*Am. J. Pub. Health* **34,** *630 (1944)*). On the one hand, it is argued that surveys have shown that a large part of the American people, many of whom are workers in industry, do not get sufficient vitamins to support optimal health and that this subnormal health is manifested as poor industrial performance, early fatigue, poor recovery from fatigue, and increased absenteeism. Since vitamins are relatively inexpensive and harmless in the usual dosage, such supplementation would constitute a valuable contribution which management can make to the health of the workers. Opposed are the facts that vitamins constitute only a few of the many dietary factors needed for health, and that a diet of properly chosen natural foods is the goal to reach to supply all the needed factors. Therefore, if any dietary essentials are needed by the workers, they should be furnished as natural foods of high nutritive value, and it is the responsibility of management to furnish adequate facilities to make this possible.

Fishbein, Tannenbaum, and Shannon (*Indust. Med.* **13,** *489 (1944)*) report the results of a study based on the former point of view. They cite the Stiebeling and Phipard survey of 1939 (*U.S.D.A. Circular no.* **507** *(1939)*) and the report of the Committee on Diagnosis and Pathology of Nutritional Deficien-

cies of the Food and Nutrition Board (*Bull. National Research Council no.* **109** (*1943*)) as justification for the assumption that a portion of their subjects were inadequately fed. Since inadequacy of the B-complex vitamins is especially likely to occur, they evaluated the change in certain common complaints after daily supplementation with a preparation containing 1 mg. of thiamin, 1 mg. of riboflavin, 5 mg. of niacin, and small amounts of pyridoxine and pantothenic acid. Although details are lacking regarding dosage and precautions to make sure that the preparations were actually consumed, it can be inferred that this supplement was taken daily for about three months by 311 subjects, and that 57 additional subjects received a placebo for the same length of time. All subjects were employed in industry, about half doing heavy work and half doing office and clerical work.

At the end of this period the subjects were asked to note any change in physiologic characteristics—constipation, mental alertness, tiredness, eyestrain, number of colds, other general illnesses, skin eruptions, appetite, and sleep—and the effect classified as favorable, unfavorable, or unchanged. The group receiving the placebo and the group receiving medication show a larger favorable than unfavorable change in all categories. This is attributed to the psychologic effect, and the authors propose that the effect of supplementation can be measured by the difference in the percentage of favorable responses in the subjects receiving vitamins and in those receiving placebos. In the case of constipation, 20 per cent in the medication group had a favorable response compared to 12 per cent in the placebo group, hence the residual 8 per cent is adduced as a true medication effect. Medication had a residual favorable effect on 16 per cent with respect to tiredness and on 10 per cent with respect to appetite and to sleep. Favorable effects were almost equal in medication and control groups with respect to the other characteristics noted.

After these results were tabulated the groups were reversed; those who had previously received placebos received medication and vice versa. The duration of the second portion of the experiment is not stated; 47 subjects receiving medication and 181 receiving placebos completed the experiment. In this second period, favorable effects on constipation, eyestrain, number of colds, other general illnesses, and skin eruptions in the supplemented group exceeded such benefits in the control group. However, mental alertness, tiredness, appetite, and sleep were improved more often in those receiving the placebo.

The data are also analyzed by following each group through both periods, a procedure which in a sense permits each subject to be his own control. When the group which received medication first is considered, the incidence of a favorable response in the supplementation period is higher than in the placebo period with respect to each of the characteristics noted. Application of the Chi square test indicates that it was extremely unlikely that these differences could arise by chance. Apparently on this basis the authors conclude that "supplementation of the average diet with vitamin B-complex had a favorable effect in the reduction of constipation and fatigue . . . a beneficial effect on mental alertness, appetite and sleep. It may also have some value in relation to eye-strain."

However, this conclusion ignores some of the published results of the study. When the group which received placebos first is considered throughout both periods, the incidence of favorable change during the placebo period exceeded such improvement during the supplementation period by 10 per cent with respect to mental alertness, 7 per cent with respect to tiredness, 13 per cent with respect to appetite and sleep. Residual differences in favor of the medication period were 5 per cent or less with respect to the other characteristics. A conclusion in accord with all the recorded findings and

with the statistical considerations involved would be that the incidence of favorable subjective response was greater to whichever pill was given first, whether it be a placebo or the supplement. It would appear that the factor of suggestion is so great that any attempt to use subjective responses to therapy in evaluating the effect of supplements is hazardous, even though a control group is used.

ALLOXAN DIABETES—A NEW TECHNIC IN NUTRITION

The discovery of Dunn, Sheehan, and McLetchie (*Lancet* **I,** *484 (1943)*) that the injection of moderate amounts of alloxan produced a selective necrosis of the islets of Langerhans in rabbits has given the laboratory worker a new and valuable technic which will undoubtedly replace to a large extent the older methods of inducing diabetes. It has also provoked much interest in the origin of spontaneous human diabetes.

Many classic studies in nutrition were carried out on animals with experimental diabetes. It may be pointed out that the concept of the glucose:nitrogen ratio arose from such experiments. The methods available in the past for the production of hypoinsulinism, namely pancreatectomy or anterior pituitary injection, have been difficult experimental procedures. The more popular procedure of phloridzin poisoning produced a satisfactory glycosuria, but the total clinical picture in no other way resembled human diabetes.

The earliest relevant observation on the toxicology of alloxan was that of Jacobs (*Proc. Soc. Exp. Biol. Med.* **37,** *407 (1937)*) who found that the intravenous administration of this drug to rabbits caused a rapidly fatal hypoglycemia. None of a long list of structurally related compounds tested shared this property. The doses of alloxan found to provoke this effect varied from 70 to 200 mg. per kilogram of body weight and the symptoms were relieved by the administration of glucose. No histologic examination was reported at that time.

Unaware of this report, Dunn, Sheehan, and McLetchie investigated alloxan as a possible renal poison and encountered the same lethal effect as that observed by Jacobs. Carefully conducted autopsies revealed only mild changes in the kidney but marked alterations in the islets of Langerhans. The islet cells were necrotic, as evidenced by pycnosis and caryolysis. The blood sugar level, after injection of alloxan, rose sharply for a few hours and then dropped markedly, with resultant hypoglycemic convulsions. In rats, some of which survived the administration of 300 to 400 mg. of alloxan per kilogram, the picture of true hypoinsulinism developed, with elevated blood glucose, glycosuria of 3.5 to 7 per cent, polyuria, polydipsia, and polyphagia, together with marked loss of weight (Dunn and McLetchie, *Lancet* **II,** *384 (1943)*). These findings suggested that alloxan initially irritated the islet tissue to produce an excess of insulin, and subsequently injured it to produce hypoinsulinism.

Bailey and Bailey (*J. Am. Med. Assn.* **122,** *1165 (1943)*) combated the early hypoglycemia of alloxan poisoning in rabbits by injecting glucose. These animals later developed full-blown diabetes mellitus which responded satisfactorily to insulin therapy. The late appearance of diabetic cataracts was noted by Bailey, Bailey, and Leech (*New Engl. J. Med.* **230,** *533 (1944)*). Ketosis and lipemia also occurred in animals not treated with insulin. In dogs the disease has been produced and studied by Goldner and Gomori (*Endocrinology* **33,** *297 (1943)*; *J. Am. Med. Assn.* **124,** *802 (1944)*). The possibility of benefit from alloxan therapy in patients suffering from insulin-producing tumors of the pancreas

has been explored by Brunschwig, Allen, Goldner, and Gomori (*Ibid.* **122,** *966* (*1943*)) and again by Brunschwig, Allen, Owens, and Thornton (*Ibid.* **124,** *212* (*1944*)).

Hughes, Ware, and Young (*Lancet* **I,** *148* (*1944*)) suggested that the early hypoglycemia after injection of alloxan resulted not from irritation of the islet cells, but rather from disintegration of these cells with liberation into the blood stream of their insulin content. This view has recently been substantiated by Ridout, Ham, and Wrenshall (*Science* **100,** *57* (*1944*)) who observed diminishing insulin content of the pancreas during the period of hypoglycemia.

The entire problem is of sufficient general interest to have received editorial comment in the leading medical journals on both sides of the Atlantic (*J. Am. Med. Assn.* **122,** *676* (*1943*); *Ibid.* **124,** *38* (*1944*); *Lancet* **II,** *389* (*1943*); *Ibid.* **I,** *154* (*1944*)). An excellent review of the subject by Joslin has also appeared (*New Engl. J. Med.* **230,** *425* (*1944*)). The medical literature has chiefly been concerned with the therapeutic applications of alloxan and with its relationship to spontaneous human diabetes. Whereas islet cell necrosis, as seen in alloxan poisoning, is not a characteristic finding in human diabetes (Dunn, Kirkpatrick, McLetchie, and Telfer, *J. Path. Bact.* **55,** *245* (*1943*)), such lesions have occasionally been seen in human autopsy material. Although alloxan, by virtue of its chemical relationship to uric acid, alloxazine, and the pyrimidines, has been suspected as a metabolic intermediate, the evidence of Cerecedo (*J. Biol. Chem.* **93,** *283* (*1931*)) tends to eliminate it from the normal oxidative pathway of naturally occurring pyrimidines.

From the point of view of the worker in the field of nutrition, however, the most interesting aspect of this development is that it affords a simple and reliable means of producing a disease state indistinguishable clinically from human diabetes. Pancreatectomy, with its incident complications, or the preparation of diabetogenic material from anterior pituitaries, promises to be superceded by the simpler technic. A single injection of about 200 mg. of alloxan per kilogram of body weight will bring about death of islet tissue within twenty-four hours, and if the initial hypoglycemia is treated with glucose, any of the common laboratory animals will develop persistent diabetes. It is expected that this simplification in procedure will stimulate renewed interest in the problem of the nutritional requirements of the diabetic animal.

TREATMENT OF CANCER WITH AVIDIN

Approximately one year ago, Rhoads and Abels reported that their attempt to produce biotin deficiency in one patient with inoperable carcinoma of the breast and one with chronic lymphatic leukemia had failed to alter the course of the two diseases (*J. Am. Med. Assn.* **121,** *1261* (*1943*); *Nutrition Reviews* **1,** *280* (*1943*)). Kaplan (*Am. J. Med. Sci.* **207,** *733* (*1944*)) has now described a similar study conducted on 10 patients with various types of malignant change. The therapeutic results were again disappointing, but since they were not entirely negative, detailed analysis of the case reports should be made.

The fundamental research which prompted these therapeutic trials has already been reviewed in this journal (*Nutrition Reviews* **1,** *51*, *247*, *271*, *280*, *561* (*1943*)). Tumors apparently differ in their vitamin requirements. Diets which protect rats from the development of butter yellow-induced hepatomas lose their protective value when biotin is added. This observation suggested that some tumors, at least, require an exceptionally large amount of biotin and might

conceivably regress or fail to develop in the usual manner if that vitamin were deficient.

Kaplan selected for his study 2 patients with myelogenous leukemia, one of carcinoma of the stomach with metastases to the abdominal wall, one of melanosarcoma of the leg with metastases, one of squamous cell carcinoma of the tongue, one of fibrosarcoma of the leg, one of Hodgkin's disease, one of cancer of the lung, one of metastatic neck cancer, and one of postoperative carcinoma of the breast with metastases. The subjects were given a diet as free as possible from foods rich in biotin. Accessory vitamins and minerals were allowed as supplements and each patient ate the whites of from thirty-six to forty-two eggs each day. This program was continued for from six months to over a year. In addition, the subject with the carcinoma of the neck (a large metastatic squamous cell mass) was treated with 2 g. of concentrated avidin per day for four months. It is significant that in no instance did the manifestations of biotin deficiency, as described by Sydenstricker and co-workers (*J. Am. Med. Assn.* **118,** *1199 (1942)*), appear. Until Sydenstricker's observations are confirmed, however, it is not fair to say that Kaplan's regimen was not rigid enough to produce an appreciable depletion of biotin. All but 3 of the patients were also treated with roentgen ray therapy.

The general condition of all subjects is reported as having been greatly improved. There was a feeling of well-being, an improved appetite, and a willingness to be up and about. The usual increasing cachexia seen in patients with cancer was notably absent. There was no significant change in the blood counts. Even though this was also true for the 2 cases of leukemia, avidin therapy caused a general relief of subjective symptoms. Recession of the tumor mass was definite enough in the patient with carcinoma of the tongue to permit him to talk much more plainly; no irradiation therapy was used. The young woman with Hodgkin's disease was subjectively improved but still had "definite clinical evidence of the disease."

Kaplan felt that the effectiveness of x-ray therapy was suggestively enhanced by the avidin administration. He withholds final opinion but stated his belief that in one of the cases of leukemia the irradiation effect was definitely prolonged. He also felt that irradiation was unusually effective in the subjects with carcinoma of the lung and melanosarcoma. It is extremely difficult to form accurate impressions, however, from so few cases. Tumors differ so much in their radiosensitivity that even the most experienced clinician makes many mistakes if he tries to guess how effective irradiation may be. The same statement can certainly also be made about myelogenous leukemia. Two subjects with comparable hematologic evidences of the disease and comparable amounts of therapy often respond differently and develop remissions which in one case may be short and the other long.

Unfortunately, Kaplan does not include any figures in his report on the urinary excretion of biotin. The degree of deficiency produced, therefore, is not known. It is possible that a portion of the subjective improvement shown by these patients may have been due to the improved nursing care they received during the study. The change noted in the carcinoma of the tongue, however, was objective. It is still conceivable that some types of malignant tumors may be favorably influenced by this type of dietary management particularly if more severe biotin depletion can be achieved. The approach should not yet be discarded.

VITAMIN E DEFICIENCY IN CHICKS

Vitamin E deficiency in chicks usually manifests itself as encephalomalacia or as exudative diathesis. These two deficiency syndromes may appear separately or together, depending on the composition of the diet. Encephalomalacia is characterized by cerebellar or cerebral edema, hemorrhages, and necrosis. Occasionally the medulla and midbrain are affected. Exudative diathesis is a condition in which plasma exudes from the capillaries giving rise to localized accumulations of fluid in the subcutaneous tissues or to more generalized edema involving the muscles and connective tissues. It has been suggested that encephalomalacia may be due simply to exudation in brain tissue, but the evidence to support this view is inconclusive.

Nutritional encephalomalacia was first observed by Pappenheimer and Goettsch (*J. Exp. Med.* **53,** *11* (*1931*)). Chicks reared on a diet of casein, corn starch, lard, salt mixture, cod liver oil, skim milk powder, yeast, and paper pulp had a short period of fairly good growth and normal behavior. Then, often with startling suddenness, signs of nervous derangement appeared. The signs most often observed were lack of coordination, coarse tremors, retraction of the head, and clonic spasms of the legs. When the chicks were handled, violent movements of the legs ("bicycling") and wings occurred. When they were not disturbed, they would often droop, close their eyes, and remain for long periods in a fixed posture. Progress of the disease was marked by increasing incoordination, ending in complete prostration, stupor, and death. Even when the prostration was most severe, however, the wings and legs were not completely paralyzed. On autopsy, edema, necrosis, and hemorrhages were found usually in the cerebellum, less frequently in the cerebrum, and at times in the medulla and midbrain. The primary cause of the lesions appeared to be hyaline thrombi of the capillaries in and about the degenerated areas. Goettsch and Pappenheimer (*J. Biol. Chem.* **114,** *673* (*1936*)) reported that chicks could be protected from nutritional encephalomalacia by the inclusion in their diet of certain edible oils, such as corn oil, cottonseed oil, peanut oil, or soybean oil. They reported, further, that following fractionation procedures, the protective factor was found in the nonsaponifiable portion of the oils. This suggested the possibility of its identity with vitamin E. When synthetic alpha-tocopherol became available, Dam, Glavind, Bernth, and Hagens (*Nature* **142,** *1157* (*1938*)) showed that it gave complete protection against the encephalomalacia.

Alimentary exudative diathesis is the name given by Dam and Glavind (*Nature* **142,** *1077* (*1938*)) to a condition which developed in chicks when they were fed a diet consisting of alcohol-extracted casein, brewers' yeast, sucrose, salt mixture, and cod liver oil. The exudates often appeared as large swollen patches on the breast and abdomen or on the legs, wings, or neck. The extravasated fluid had approximately the same composition as that of normal plasma. The affected tissues, particularly the adipose tissue, were usually reddish in color due to fine diffuse hemorrhages. Microscopically there was edema, slight extravasation of red cells and migration of white cells in the affected tissue, and a milk eosinophilia (Dam and Glavind, *Skand. Arch. Physiol.* **82,** *299* (*1939*)). Bird and Culton (*Proc. Soc. Exp. Biol. Med.* **44,** *543* (*1940*)) reported data which indicated that the localization of the exudate could be influenced by modifications of the diet. Using a ration of skim milk powder, sucrose, and salts with a supplement of cod liver oil, they produced a condition in which in addition to the usual exudates there was a considerable accumulation of fluid in the pericardium and peritoneal cavity. Dam and Glavind (*Nature*

143, *810 (1939)*) demonstrated that vitamin E protects against the exudative diathesis.

It should be noted that the chick diet used by Pappenheimer and Goettsch rarely causes exudative diathesis, while that employed by Dam and Glavind only occasionally leads to encephalomalacia. Considerable evidence has been accumulated in recent years to indicate that variations in the diet, wholly unrelated to the content of vitamin E, may greatly influence the severity of deficiency signs as well as determine the nature of the signs which appear. Some information is available concerning the specific dietary ingredients which are important in this regard. Dam and Glavind (*Science* **96,** *235 (1942)*) noted that the addition of sodium chloride to their diet accelerated the appearance of exudates. They reported also that the administration of cholesterol had an accelerating effect on the appearance of this syndrome, while inositol and lipocaic had a delaying effect. Dam (*Proc. Soc. Exp. Biol. Med.* **52,** *285 (1943)*) demonstrated that the development of exudates and the appearance of encephalomalacia are both dependent on the presence of highly unsaturated fatty acids in a vitamin E deficient diet. This work has been previously reviewed (*Nutrition Reviews* **1,** *381 (1943)*). In a later publication, Dam (*J. Nutrition* **27,** *193 (1944)*) has presented the result of more extended observations. His data support the following conclusions: (1) Purified diets containing only traces of fat rarely produce exudates and never induce encephalomalacia. (2) Both deficiency signs are accelerated by highly unsaturated fatty acids, but the kind and the amount administered influence the type of deficiency signs which appear. (3) The form of carbohydrate in the diet and the protein-carbohydrate ratio are important. (4) The tendency to exudates is enhanced by those inorganic salts which tend to accumulate in the extracellular fluid. (5) Inositol counteracts both encephalomalacia and exudative diathesis; lipocaic counteracts the latter syndrome only. (6) Cholesterol hastens the appearance of the exudates or counteracts the encephalomalacia, depending on the other constituents of the diet.

The diets used by Dam in these investigations were modifications of his exudate-producing basal diet 182, which consists of alcohol-extracted casein 15 per cent, ether-extracted dried yeast 10 per cent, sucrose 54.6 per cent, gelatine 8 per cent, gum arabic 5 per cent, salt mixture 7.2 per cent, cod liver oil 5 per cent, l-cystine 0.1 per cent, choline chloride 0.1 per cent, and a synthetic with vitamin K activity 1 mg. per cent.

This basal diet was effective in producing exudates as a regular occurrence and in producing encephalomalacia much less regularly. Data concerning the influence of the fat in the development of these deficiency signs were obtained by feeding various modifications of the basal ration. The data obtained indicated that fat is necessary for the development of both exudates and encephalomalacia and that certain fats (or more specifically the highly unsaturated fatty acids present in them) favor one deficiency sign more than the other. For example, deficiency signs appeared but rarely when cod liver oil was omitted or was replaced by an equivalent amount of its nonsaponifiable fraction. The saponifiable fraction was active as was a commercial preparation of the C_{20} unsaturated fatty acids. Oleic acid was inactive. If 30 per cent of lard replaced an equal amount of sugar and the cod liver oil was omitted, exudates and encephalomalacia developed almost together and with almost equal frequency. When hog liver fat or its fatty acids replaced cod liver oil in the basal diet, there was an almost complete shift from exudative diathesis to encephalomalacia.

The type of carbohydrate, the protein: carbohydrate ratio, and the level of sodium chloride in the diet also influenced the appearance of deficiency signs. Corn starch was less effective than sucrose in the production of exudates, but when the diet contained

sufficient fat such as lard, the use of starch greatly increased the incidence of encephalomalacia and made it the dominant deficiency sign. When all of the carbohydrate in this diet was replaced by casein, encephalomalacia was even more greatly favored. Further data suggested that there is an optimal protein:carbohydrate ratio for the development of exudates. A casein:corn starch ratio of 15 per cent:54.6 per cent caused an earler onset and a higher incidence of this deficiency sign than either a 7.5 per cent:62.1 per cent or a 35 per cent:34.6 per cent ratio. When the level of sodium chloride in the diet was increased, the exudates appeared much earlier than in the controls. On the other hand, the addition of potassium chloride caused no such acceleration. This is in agreement with the common clinical experience that salts which tend to accumulate in the extracellular fluids enhance a tendency to edema.

The author repeated some of the earlier observations of Dam and Glavind on the effects of cholesterol, inositol, and lipocaic on exudative diathesis and extended them to include the effects on encephalomalacia. He found that cholesterol hastened the appearance of the exudates when the diet contained 5 per cent of cod liver oil, but not when it contained 30 per cent of lard. With the latter diet, cholesterol decreased the incidence and delayed the onset of encephalomalacia. Inositol was found to counteract both deficiency syndromes, while lipocaic counteracted exudates only. This is particularly interesting in view of the report of Gavin, Patterson, and McHenry (*J. Biol. Chem.* **148,** *275 (1943)*) on the lipotropic effects of inositol and lipocaic in rats. They found that inositol is effective in preventing the fatty livers caused by feeding cholesterol in high fat diets and also those caused by feeding biotin. Lipocaic, on the other hand, is active in preventing the latter type of fatty liver only.

The investigations of Dam appear to represent a distinct contribution to our knowledge of the physiologic role of vitamin E. Much of the data presented indicate that there is a connection between fat metabolism and the appearance of vitamin E deficiency signs in chicks. Not only the influence on the production of these syndromes of fats, fatty acid fractions, and cholesterol, but also the effects of such lipotropic substances as inositol and lipocaic support this thesis. It will be of great interest to ascertain whether there is a similar relationship in other animals particularly owing to the fact that the vitamin E deficiency signs in as closely related a species as the duck is muscular dystrophy rather than encephalomalacia or exudative diathesis.

VITAMINS IN GERMINATED PEAS AND BEANS

Some degree of scurvy is said to have appeared in every army in every major war of history, and the existence of other avitaminoses would also seem probable. Of course the abundance of synthetic vitamins at the present time makes the problem much less acute than formerly, even though situations still arise in which men are forced to subsist on canned meats and grain products that no longer supply an optimal amount of B-vitamins, and on canned or dehydrated vegetables that have lost much of their original content of vitamin C. Thus an accessory source of these vitamins is still desirable.

Among the foods commonly transported by military groups in restricted areas (nutritionally speaking), the dried legumes would appear to be one of the best potential sources of vitamin C and of certain other vitamins. Dried beans and peas are relatively light in weight and compact in bulk, and in themselves are of high nutritional value.

As early as 1912 germinated seeds were proposed as a source of the antiscorbutic vitamin in the military diet, although this recommendation does not seem to have been followed. Scurvy became a serious menace among the British and Indian troops in the Mesopotamian campaign of 1915 to 1916; after the damage was done, the problem was studied more extensively. Chick and Delf (1919) then reported that dried peas and lentils suitable for transport could be made to develop much "antiscorbutic stuff" when germinated for use as required. During the present war the Australian army has issued instructions for the proper sprouting of the blue boiler pea.

Studies of the B-vitamins have been made by Rose and Phipard (*J. Nutrition* **14,** *55 (1937)*) who noted that the riboflavin content of germinated peas and Lima beans was definitely higher in 14 day old seedlings than in the dry seed. Vitamin B, however, seemed to decrease during the germination process. Burkholder (*Science* **97,** *562 (1943)*; *Nutrition Reviews* **1,** *357 (1943)*) summarized information on the vitamin content of many different kinds of sprouted grains. Riboflavin, niacin, pyridoxine, and biotin were all found to increase on germination, while thiamin remained unchanged. Many of the extra vitamins were retained when the sprouts were properly dried.

A more recent study of the vitamin content of germinated legumes has been made by French and co-workers (*J. Nutrition* **28,** *63 (1944)*). The following varieties were studied: Peas—Alaska, Wrinkled, Blackeye Cowpea; Soybeans—Peking, Bansei-1, Edsoy, Clemson, Higan-B, Easycook; Beans—Navy, Baby Lima, Red Kidney, Pinto. The seeds were placed in sterile burlap bags large enough to permit a fivefold increase in volume. They were then immersed in tap water for eight hours after which they were suspended above a drip pan in front of an open window allowing free circulation of air. Longer periods of initial soaking were found to accelerate the appearance of rot. After the initial softening, the seeds were immersed in fresh water for twenty minutes three times daily at eight hour intervals. All of the various soybeans and peas sprouted well; the pinto beans had a germination count of 84 per cent, the Lima beans of 81 per cent. However, only 35 per cent of the navy beans sprouted, while the kidney beans failed to sprout at all.

The sprouts were then ground, and their contents of ascorbic acid, riboflavin, thiamin, and nicotinic acid determined by established methods. Sprouting caused a marked increase in ascorbic acid and a fair increase in riboflavin and nicotinic acid, but none in thiamin. The peas were found to produce the greatest amounts of new vitamin on germination, while the soybeans also proved to be of value, although less efficient than the peas. Other types of beans showed a tendency to rot, whereupon the production of new vitamins ceased.

Peas and soybeans prepared in the manner described are said to have an excellent flavor and to be highly palatable provided they are less than two inches in length. As an illustration of the nutritive significance of these materials, French *et al.* have calculated that a 100 g. serving of sprouted peas would contain a minimum of 25 mg. of ascorbic acid before cooking. The content of the other vitamins does not constitute as large a proportion of the daily vitamin requirement, but it is also appreciable. Certainly the emergency value of sprouted legumes deserves to be more widely recognized.

NOTES

Letters To The Editor

Dear Sir:

I feel that Nutrition Reviews has supplied most satisfactorily a real need, not only for the layman, but also for the trained nutrition worker, for condensed reviews on timely subjects which you have presented in a very interesting style. I should like to offer some comments on several articles which have appeared on the comparative nutritive value of fats.

In a recent article on "Nutritive Value of Butterfat, Vegetable Oils and Oleomargarines" (*Nutrition Reviews* **2,** *165* (*1944*)) it was stated that, as a result of the recent experiments of Boutwell, Geyer, Elvehjem, and Hart, "If the deductions are right, however, they indicate that butterfat may be nutritionally superior to vegetable oils only during comparatively brief periods of human life: during infancy or at times when, for medical reasons, a patient may be placed on a predominantly milk diet." It should be pointed out, however, that this statement is open to question since the above-mentioned experiments were obtained on synthetic diets where lactose was present not in the proportions ordinarily found in milk, but in considerably higher percentage. When lactose is present in the amount ordinarily found in milk we have recently found no differences in growth rate in 21-day weanling rats, irrespective of whether the fat is butterfat, corn oil, cottonseed oil, olive oil, peanut oil, soybean oil, or a margarine, provided that the fat-soluble vitamins are supplied. These results you have reviewed in considerable detail in the current issue (*Nutrition Reviews* **2,** *267* (*1944*)).

Moreover, the application of these results to human nutrition may be limited, since as you point out in the most recent review, butter may actually be inferior to vegetable fats in the nutrition of premature infants. Certainly there is as much difference between the composition of *human* milk fat and cow's milk fat as between the various vegetable fats and human milk fat (Baldwin and Longenecker, *J. Biol. Chem.* **154,** *255* (*1944*)). You have suggested that possibly the fact that the "basal ration of skimmed milk powder. . . contained 1.1 per cent of lipids, presumably butterfat, while the work at Wisconsin was done on fat-free milk powder or on synthetic basal rations" might account for the better results on the vegetable oils. However, in our original report where this fact was originally pointed out we also indicated that "In the earliest tests of Schantz *et al.* ('40) where liquid skimmed milk was used, no such extraction was employed. It was in these experiments where the most marked variations in growth occurred at three weeks." Also, it should be added that the amount of high molecular fats would necessarily be extremely small in diets where approximately 30 parts of the fat were added to 70 parts of unextracted milk powder. The total daily intake of such saturated high molecular fats from such sources could scarcely exceed 10 mg. Since most of these fatty acids in this fraction are identical with those present in vegetable fats, those acids characteristic for butterfat and at present not identified would necessarily be present in extremely minute amounts.

As you have indicated in your review, we have criticized "the idea that increased appetite for food in *ad libitum* feeding experiments must necessarily indicate a superior food." We know of no experiments which offer definite proof of such a generalization and so would question the statement which follows the above quotation, viz.: "The history of animal nu-

trition, however, bears this out." Certainly, the appetite of children for candy and sweets is not to be construed as an indication of the superior nutritive value of these products.

There are several additional important facts which were not available to the reviewer at the time this article was written. A marked difference has been shown in two species of rats to diets high in lactose (Ershoff and Deuel in *J. Nutrition*, in press). Such high-lactose diets were fatal in all cases to rats of the Long-Evans strain but to a much less degree in the University of Southern California strain.

Also, recent experiments of Zialcita and Mitchell (*Science* **100,** *60 (1944)*) have shown identical nutritive values of butterfat and corn oil in rats weaned at 7 and 14 days. These data are similar to unpublished results from our laboratory on rats weaned at 14 days of age and fed on skimmed milk containing the various fats employed in our earlier experiments. These results with prematurely weaned rats would seem to indicate that under the conditions of the present experiments the nutritive value of butterfat is not related to age, as was suggested in an earlier review on the "Nutritive Value of Butterfat" (*Nutrition Reviews* **1,** *358 (1943)*).

Sincerely yours,

H. J. Deuel, Jr.,
Professor of Biochemistry and Nutrition,
University of Southern California,
Los Angeles.

The Canadian Council on Nutrition

The ninth meeting of the Canadian Council on Nutrition was held in Ottawa. Two special guests, Dr. Russell M. Wilder, vice-chairman, and Dr. Frank L. Gunderson, executive secretary of the Food and Nutrition Board of the United States National Research Council, were present. They outlined the work of the Board from its beginning up to the present time.

The following reports were received and discussed: school lunches, Canada's food rules, water, iodized salt, milk, Canada approved flours and bread, shopping lists, Swift fellowship in applied nutrition, food analysis, surveys, etc.

The most important resolutions arising from the meeting were: (1) That each province should employ at least one full-time nutritionist. (2) That the government should devise and implement a national food policy to insure that every Canadian receive sufficient food to meet nutritional requirements; the Canadian Council on Nutrition offers its services as an advisory body for such a plan. (3) That all white bread offered for sale or in public eating places should be made from Canada approved flour and that encouragement be given to making Canada approved flour available for household use. (4) That a committee on shopping lists should be established and remain until the next meeting of the council. (5) That all organizations represented on the Council use the food consumption table when available and that a representative of the Canadian Dietetic Association be added to the committee. (6) That the committee on school lunches proceed with their report, which will be given to the Minister of Pensions and National Health, urging that money be made available for the purpose of improving the nutritional status of schoolchildren by means of an adequate school lunch program throughout the Dominion. (7) That representatives of organizations interested in nutrition, not only report meetings of the council to their organization, but also report views of their organizations to the Canadian Council on Nutrition. (8) That a $50,000 annual grant be made available for investigations on nutrition.

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The Nutrition Foundation was organized by food and related manufacturers to develop and support a comprehensive research and educational program in the science of nutrition. The Foundation functions chiefly through grants in support of research in university centers where there are strong graduate schools in the basic sciences.

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CONTENTS

(*Continued from Front Cover*)

Vitamin B-Complex and Hard Work 334

Nutritional Quality of Processed Foods 336

Dietary Factors that Influence Carcinogenesis 338

Methionine and Liver Necrosis in Man 340

Vitamin Pills for Industrial Workers 342

Alloxan Diabetes—A New Technic in Nutrition 344

Treatment of Cancer With Avidin 345

Vitamin E Deficiency in Chicks 347

Vitamins in Germinated Peas and Beans 349

Notes 351

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The Editorial Staff has been carefully selected so that the publication will merit in reasonable degree, the confidence of the medical profession and others who work directly with the public in the field of nutrition. The service provided by the publication is distinct from that of an abstract journal, a review for laymen, or an extensive scientific review. Since the reviews as originally prepared by a member of the Editorial Staff are frequently modified by special referees and may be further modified by the Editorial Office in preparing final copy for the press, the Editorial Committee feels that it is preferable not to affix the names of Editorial Staff members to individual reviews. There is thus a high degree of group responsibility on the part of the Editor and Assistant Editors.